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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,421	06/30/2005	Mario Clerici	62526US(50221)	5505

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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
04/21/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/516,421	**Applicant(s)** CLERICI ET AL.	
	Examiner SARAE BAUSCH	**Art Unit** 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 April 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *5* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3 and 4*.
   Claim(s) withdrawn from consideration: *5-20*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Sarae Bausch/
Primary Examiner
Art Unit: 1634

Continuation of 3. NOTE: The proposed amendment to the claims present additional claims but do not cancel any finally rejected claims..

Continuation of 11. does NOT place the application in condition for allowance because: The response disagress with the 112, 1st enablement rejection and request the rejection be withdrawn. The response asserts that the specificaiton must be accepted as providing an enabling disclosure unless the examiner has evidence showing that the truthfulness of such statements is in doubt and assert that IL10A and IL6C alleles are associated with alzheimers disease. The response asserts that applicants specification clearly associates Alzheimers disease with IL-10 -1082A, IL-6 -174C and points to table V and VI. However, as addressed in the previous office action, the evidence in the art teaches the unpredictability of associating IL-10 -1082A allele with increase or decreased risk of alzheimers disease in any ethnic population. Thus although the specification presents a small population and its genotyping association and frequency in a small AD population, this does not outweigh the proponderence of evidence in the art that teaches the unpredictability of -1082 IL-10A allele and its association with AD in any ethnic group.

The response asserts that although Bagnoli and Capruso prportedly differ from the findings described by Applicant Bagnoli and Capruso fail to provide reason to doubt the objectived truth of the statements contained within Applicants specification. The response points to Bagnoli teaching the role of IL-10 gene is AD susceptibility may be limited to certain populations indicating the need of further studies and points to Capruso that teaches that further studies on larger and different populations controlling for ethnic and geographic variability should be conducted. It is noted that both Bagnoli and Capruso demonstrate the unpredictability and undue experimentation necessary to perform the claimed invention. The response asserts that a finding of a particular marker that has been positively associated with disease in a small sample of carefully and closely matched individuals is not negated by contrary observations in a large population of unmatched inviduals. However, the preponderance of evidence, as demonstrated by Bagnoli and Capruso, suggest that the required association of the IL-10 -1082A allele with AD is not robust and would not be reliably applicable to any population other than the actual study subjects of the instant specification. Additionally the claims are not limited to closely matched individuals but are broadly drawn to any human subject thus the teachings of Bagnoli and Capruso demonstrate the unpredictability and undue experimentation needed to perform the claimed invention.

The response asserts that Applicants have provided literature that confirms the studies upon which Applicants lcaimed invention is based. Applicants point to Combarros, Ma, and Infante. Each of these references were previously considered and addressed on pages 14-16 of the office action mailed 11/04/08. Specifically, Infante teaches that -1082A alone is not predictive of AD, Ma teaches the unpredictability of -1082A allele with AD in different ethnic populations and Combarros does not confirm the teachings in the specification as Combarros teaches only a small effect was seen with heterozygous -1082A allele. Thus as stated previously Combarros, Ma and Infante do not provide evidence that the claimed invention of any risk of AD in any population of either the homozygous or heterozygous presence of -1082A IL-10 allele is enabled and infact each provide further evidence of the unpredictability and undue experimentation that is necessary to perform the claimed method.

The response asserts that none of the references, Kroese, Hattersley, Ionnidis, and Hegele are specifically relelveant to methods that are useful or predictive of AD in a human subject and thus fail to support the enablement rejection. It is noted that these references were cited to demonstrate the general state of the art and unpredictability of associating a specific genotype to a specific disease. These references demonstrate that in larger, replicated studies the association of a specific genotype to a disease are not necessarily associated with a specific disease.

The resposne asserts that conducting analysis of 168 subjects is not unduly burdenson and multiple comparisons is not undue experimentation because one of skill in the art could readily identify subjects having allelic avariants present at one or more snps. The response asserts that one of skill in the art could readily identify subjects having a predisposition to AD by analysing a DNA sample taken from a subject and determining the alleleic variant at position -1082 of IL-10. This resposne has been thoroughly reviewed but not found persuasive. It is noted that the examiner agrees that determining the allelic variant at position -1082 of IL-10 in a biological sample is not undue experimentation, however the claims are not limited to merely determining an allelic variant, the claims require the association of the allelic variant -1082 A with predisposition of AD, thus the claims require the predictabily correlation of -1082 A IL-10 with AD and the prior art demonstrates the unpredictability and undue experimentation necessary to perform the claimed invention, specifically the art demonstrates that larger studies in different populations are necessary to determine an association between IL-10 -1082 genotype and AD. Thus the preponderance of evidence demonstrates the unpredictability and undue experimentation needed to perform the claimed method.

With regard to applicants remarks with respect to the 112, 2nd rejection and objection to the specification, the response is drawn to the proposed amendment, which has not been entered, thus the remarks are moot and will not be addressed..